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Review Article

TRANEXAMIC ACID AND TRAUMA: CURRENT STATUS AND KNOWLEDGE GAPS WITH RECOMMENDED RESEARCH PRIORITIES

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ABSTRACT—A recent large civilian randomized controlled trial on the use of tranexamic acid (TXA) for trauma reported important survival benefits. Subsequently, successful use of TXA for combat casualties in Afghanistan was also reported. As a result of these promising studies, there has been growing interest in the use of TXA for trauma. Potential adverse effects of TXA have also been reported. A US Department of Defense committee conducted a review and assessment of knowledge gaps and research requirements regarding the use of TXA for the treatment of casualties that have experienced traumatic hemorrhage. We present identified knowledge gaps and associated research priorities. We believe that important knowledge gaps exist and that a targeted, prioritized research effort will contribute to the refinement of practice guidelines over time.

KEYWORDS—Tranexamic acid, trauma, efficacy, safety, research requirements

INTRODUCTION

Tranexamic acid (TXA) is an antifibrinolytic drug that has been used for decades for indications such as dental extraction in patients with hemophilia. It has also been widely used to decrease blood loss in surgeries, including cardiac surgery and joint replacement (1–5). Most recently, the potential for use of TXA in trauma has been of particular interest (6–8). In 2010, the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) investigators reported data from a randomized trial of more than 20,000 patients who had sustained trauma, showing that the use of TXA reduced in-hospital 28-day all-cause mortality from 16.0% to 14.5% and death due to bleeding from 5.7% to 4.9% (6). More recently, Morrison et al. (7), in a retrospective database analysis of 896 injured patients in a military surgical hospital in Afghanistan, reported an even greater mortality reduction (from 23.9% to 17.4%) with use of TXA.

These findings have engendered substantial interest in TXA in both the civilian (8) and military trauma communities. The British military incorporated TXA into formal clinical practice guidelines in 2010 (7). More recently, the US Military incorporated the use of TXA for trauma into clinical practice guidelines (9), as well as into guidelines for tactical combat casualty care (10, 11). Current military guidelines have been carefully developed based on all available information and incorporate extensive monitoring and quality improvement measures.

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The US Department of Defense continuously strives to advance and improve treatment of combat casualties. At the request of the Office of the Assistant Secretary of Defense for Health Affairs and the Joint Program Committee for Combat Casualty Care Research, the committee (composed of the authors) conducted a review and assessment of knowledge gaps and research requirements regarding the use of TXA for the treatment of casualties that have experienced traumatic hemorrhage. We present the identified knowledge gaps and associated research priorities. We believe that important knowledge gaps exist and that a targeted, prioritized research effort will contribute to the refinement of practice guidelines over time.

METHODS

Those performing the evaluation and providing recommendations included committee members (authors) as well as invited subject matter experts, including both US and British medical officers who were involved in the development of practice guidelines and who had experience with TXA in trauma, and experts involved with the CRASH-2 study. Recommendations were developed through a series of meetings, teleconferences, and electronic communications between October 2010 and October 2011. The evaluations and recommendations reported here are the opinions of the authors and are not the official position of the US Department of Defense.

TRAUMA TRIALS

The available data provide evidence that use of TXA in trauma provides a reduction in all-cause mortality, with the most significant effect in reducing deaths due to hemorrhage. This, combined with the safety profile of TXA in other indications, argues strongly for the incorporation of TXA into clinical practice guidelines for trauma, as has been done by the US Military and others. However, important questions remain with respect to the use of TXA in trauma (Table 1).

A large randomized prospective clinical trial (CRASH-2) of 20,211 patients in civilian hospitals, almost exclusively in the developing world, found an in-hospital 28-day overall survival benefit with TXA (14.5%), compared with placebo (16.0%; $P = 0.0035$) (6). Similarly, death attributed to bleeding was reduced from 5.7% to 4.9% ($P = 0.0077$). The survival benefit occurred only if TXA was administered within 3 h of injury (12). Despite the very large sample size and extraordinary effort of the CRASH-2 trial, several aspects of the design and results leave certain knowledge gaps as they pertain to military medicine and to civilian medicine in the developed world. Just 1.4% of patients were from institutions in countries (none from the United States) where it was likely that trauma resuscitation and care with all therapies, including blood components, were consistently practiced. Lack of clarity of patient care and monitoring, lack of injury severity or revised trauma scores, lack of data on blood loss, and lack of systematic reporting of serious adverse events make independent assessment of the report difficult. Furthermore, only 50.8% of patients were transfused, and less than half met the blood pressure or heart rate entry criteria. These issues raise questions regarding the robustness and applicability of the primary mortality and safety findings.

The issue of applicability of data for the use of TXA as an adjunct to current trauma care and military injuries was addressed by Morrison et al. (7) in a retrospective analysis of prospectively collected observational data from 896 consecutive patients in a military hospital in Afghanistan. The data were accumulated during 2009 and 2010, for 377 civilian and 519 military patients who were severely injured and transfused at least one unit of red blood cells within 24 h of admission, with more than a third transfused massively (defined as ≥10 units of blood). In this population, use of TXA (293 patients) was associated with reduced 48-h all-cause mortality (11.3% vs. 18.9%; $P = 0.004$) and reduced in-hospital mortality (17.4% vs. 23.9%; $P = 0.030$) for all patients. Similar results were observed among patients who were massively transfused. However, no changes in 24-h mortality were observed. As is common for retrospective database analyses, there were some confounding factors, including a change in clinical practice during the period examined (from administering TXA according to physician discretion to protocol-driven care) and a statistically greater use of all blood components (red blood cells, fresh frozen plasma, platelets, and cryoprecipitate; each $P \leq 0.001$) in the TXA group. The increased blood component use could reflect the more seriously injured group (supported by worse revised trauma [$P = 0.01$] and injury severity [$P < 0.001$] scores) or be a consequence of survivorship.

In both trauma studies, safety signals were observed that suggest potential adverse events associated with use of TXA, perhaps in selected patient subpopulations or under certain conditions. The CRASH-2 trial reported that mortality due to bleeding increased from 3.1% to 4.4% ($P = 0.0049$) in the TXA-treated patients if treatment was initiated more than 3 h after injury (12) Morrison et al. (7) noted a statistically significant increase in pulmonary embolism (TXA: 2.7% vs. no TXA: 0.3%; $P = 0.001$) and deep vein thrombosis (TXA: 2.4% vs. no TXA: 0.2%; $P = 0.001$) in TXA-treated patients.

TRANEXAMIC ACID IN OTHER SURGICAL INDICATIONS

It is useful to consider the longer experience with the use of antifibrinolytics in other surgical settings, such as cardiac and orthopedic surgery. Tranexamic acid (Cyklokapron) was approved by the Food and Drug Administration in 1986 for use in patients with hemophilia to reduce or prevent hemorrhage with tooth extraction and reduce the need for replacement therapy (coagulation factors). That remains its sole indication. Tranexamic acid was also approved in an oral form for menorrhagia in 2009 (Lysteda). Thus, any other use of TXA in the United States, including for trauma, remains "off-label."

Following the withdrawal of aprotinin (Trasylol; Bayer) from the market because of concerns about renal and cardiovascular safety (13) and increased mortality (14) in 2007, use of TXA in surgery has increased, and a number of retrospective studies have compared lysine analogs (primarily TXA) to aprotinin. Henry et al. (2) published findings of a large meta-analysis and concluded that the evidence favored use of lysine analogs because they were almost as effective as aprotinin, were cheaper, and did not increase mortality. However, the meta-analysis did not demonstrate statistically improved safety of TXA or ϵ-aminocaproic acid (EACA) over aprotinin. Martin et al. (1) reported on a series of nearly 600 cardiac surgery patients treated with aprotinin followed by a similar number of patients treated with TXA. They found that the incidence

TABLE 1. **Consensus list of prioritized knowledge gaps/research requirements**

Category	Knowledge gaps/research requirements
Priority 1	
Safety	Further information specifically on the potential negative effects that were identified in CRASH-2 and MATTERS. First, the increased risk of death from bleeding in the group that received initial TXA treatment 3 h or more after injury in CRASH-2 (6, 12). Second are the increased thrombotic events observed in MATTERS (7). There were significant increases in both deep vein thrombosis and pulmonary thromboembolism with the use of TXA in that study.
	Further investigation of thromboembolic risk, especially in the context of damage-control resuscitation.
	Potential complications and contraindicated subpopulations of trauma patients, including patients with TBI and potential impact of TXA on postoperative seizures.
	Evaluation of patients who die after TXA—detailed examination for microthrombi, etc.
Animal models	Animal models need to be developed/identified to support the efficacy, safety, and mechanistic studies of TXA.
Additional proof of efficacy and definition of what patients may benefit from TXA	Properly designed trials to establish efficacy in patients treated to modern civilian and military trauma standards.
	Better definition of which patients will benefit from TXA (e.g., penetrating wounds to the torso without shock; penetrating wounds to the torso with shock; polytrauma without shock; polytrauma with shock; isolated closed-head trauma; closed-head trauma with polytrauma).
Mechanism of action	Information on the mechanism of action in traumatic hemorrhage. Multiple mechanisms have been proposed but not proven.
Efficacy and safety in isolated parenchymal brain injury	Information is needed on potential efficacy and safety in isolated parenchymal injury/bleeding of the brain.
Prehospital use (in tactical combat casualty care)	Potential for use in the prehospital setting, with delayed evacuation, limited other supporting products (maybe no blood products or only plasma), and very early administration/alternative dose and timing.
	Interactions with other prehospital resuscitation fluids and agents, impact of storage in the field environment.
	Compatibility with the remote damage-control resuscitation concepts.
Priority 2	
Temporal changes/optimal treatment window	Efficacy and safety of TXA with administration beginning at various times after trauma. What should be the "cutoff" time for TXA (what is the optimal window for administration)?
TXA in combination with blood products	Is the effect one of TXA, or TXA in combination with blood products, etc.?
Routes of administration	Potential routes of administration: intravenous, oral, IO", transmucosal.
Priority 3	
Interactions with inflammatory and coagulation systems	Inflammatory and coagulation patterns. Changes over time with TXA starting at various times following injury.
Dosing	All available data are based on one dosage regimen; could other regimens improve efficacy and safety, or worsen efficacy and safety? How are pharmacokinetics affected by trauma?
Use with standard resuscitation fluids	Potential for use of TXA in combination with other fluids (e.g., Hextend).
Microcirculation	Effects of TXA on microcirculatory blood flow.
Drug interactions	Interaction with thromboprophylactic, prohemostatic (e.g., recombinant activated factor VII), antiseizure, or other drugs.

of acute myocardial infarctions was lower in patients who received TXA than in those who received aprotinin (2.0% vs. 5.8%; $P = 0.027$). In another retrospective case series, there was no overall difference in the incidence of thrombotic complications, whereas in the subset of open-heart-surgery patients, myocardial infarctions were increased with TXA, suggesting a possible difference in TXA-related thrombotic risk in specific surgical procedures (4). Late ischemic strokes were elevated in patients who received aprotinin. More recently, a comparison of TXA and EACA revealed no difference in the incidence of transient ischemic events between cardiac surgical patients who received either of the two drugs (5).

Kagoma et al. (3) conducted a meta-analysis of randomized trials that examined the use of antifibrinolytic therapy in total hip replacement and total knee arthroplasty. They reported overall reduction in transfusion for TXA as well as for aprotinin and EACA. There was no increase in venous thromboembolism with any of the drugs. Orthopedic surgeries such as total

hip replacement are often performed in patients with increased thrombotic risk. Therefore, these data are suggestive of a good safety profile that may extend to trauma patients. However, in this report, well more than half of the patients who were treated with TXA also received preoperative antithrombotic therapy, effectively decreasing the risk in this population and diminishing the ability to interpret thrombotic risk of TXA. The authors concluded that although the data are promising, further studies are needed to adequately assess the thrombotic risk associated with the lysine analogs in orthopedic surgery (3).

THROMBOTIC RISK

The failure of most studies to demonstrate an increased risk for thrombotic complications after TXA suggests that these complications are not frequent. The observation that TXA use in combat trauma resulted in increased incidences of both deep vein thrombosis and pulmonary thromboembolism was suggested by Morrison et al. to be due to the increased injury severity score (ISS) in the patients who received TXA (ISS 25.2 vs. 22.5, for TXA and no TXA, respectively) (7). This is a likely possibility, considering the known relationship between ISS and thrombotic risk (15, 16). However, it cannot be ruled out that the effect was due to the drug and that the incidence of thrombotic complications after TXA in trauma may be greater than that in other applications of TXA.

POSTOPERATIVE SEIZURES

An increase in postoperative seizures following the use of TXA in cardiac surgery has been reported with increasing frequency. This may be due to the action of TXA as a γ-aminobutyrate receptor antagonist inducing hyperexcitability by blocking γ-aminobutyrate–driven inhibition of the central nervous system and decreasing the seizure threshold (17). Recent studies have documented increases in nonischemic postoperative seizures with the use of TXA in cardiac surgery. Martin et al. (1) reported an increase in seizures from 1.2% in cardiac surgical patients who received aprotinin to 4.6% in patients who received TXA ($P < 0.01$). In a follow-up study, these investigators also found that the rate of postoperative seizures was increased ($P = 0.02$) with TXA (7.6%) as compared with EACA (3.3%), another lysine analog (5). In another study, the incidence of seizures increased from 0.9% to 2.7% ($P = 0.05$) (4). Murkin et al. (18) observed that postoperative convulsive seizures increased from 1.3% to 3.8% coincident with the transition from aprotinin to TXA in cardiac surgery. They reported that no evidence of brain ischemic, metabolic, or hyperthermia-related causes was evident, suggesting that the effect was attributable to TXA. Keyl et al. (19) reported a 19-fold increase ($P < 0.01$) in postoperative seizures when TXA was used during aortic valve replacement, compared with when EACA was used (6.4% vs. 0.6%, respectively). More recent reports confirmed earlier findings and also suggested that the effect is dose-dependent (20–22). A consistent finding has been that the effect is most pronounced in open-heart procedures. The increased rate of postoperative seizures has led some groups to reduce or eliminate the use of TXA in favor of EACA for cardiac surgery (5, 19).

It is not known whether this proconvulsant effect occurs in trauma. The dosages reported for trauma use were a total of 2 g over 8 h in the CRASH-2 trial (6) and 1 g with repeat dosing at physician discretion in the MATTERS (Military Application of Tranexamic Acid in Trauma Emergency Resuscitation Study) analysis (7). Assuming a body weight of 75 kg and the dose regimen described in CRASH-2, this equates to an approximate dose of 27 mg/kg. The reported doses that resulted in increased seizures following cardiac surgery were approximately 24 mg/kg (22), 54 mg/kg (1), 61 to 256 mg/kg (18), and 100 mg/kg (4, 20). Martin et al. (5), Keyl et al. (19), and Manji et al. (21) reported that TXA doses of approximately 5 g (body weight conversions not reported) were associated with increased seizures. Considering that dosing in some studies was similar to or only 2-fold higher than the doses used in trauma, it cannot be assumed that the effect is not present in trauma. Especially in the military setting, hemorrhagic shock may occur with polytrauma including concomitant traumatic brain injury (TBI). The potential seizure-inducing effects of TXA in this setting are unknown. Current recommendations for the treatment of TBI include minimizing seizures with anticonvulsant drugs (23). Reports from trauma studies to date have not discussed seizure rates following TXA administration. A single study that examined the use of TXA in TBI (24) was not able to rule out either negative or positive effects, and no information for seizures was included in the article. It will be important to understand the potential seizure-inducing effects of TXA in trauma, as well as potential drug interactions with anticonvulsant medications used in TBI.

MECHANISM OF ACTION

As an antifibrinolytic lysine analog (MW 157.2), TXA binds to plasminogen and plasmin, the central enzyme in fibrinolysis. It inhibits plasminogen activation but does not specifically impair the enzymatic activity at the catalytic site (25). It is well accepted that TXA exerts an antifibrinolytic action to reduce blood loss, especially in conditions where fibrinolysis or hyperfibrinolysis is a factor. Thromboelastography or rotational thromboelastometry may identify fibrinolysis, possibly making it a useful tool in identifying patients who may benefit from the use of an antifibrinolytic agent, such as TXA. However, thromboelastography or rotational thromboelastometry would not necessarily be useful with respect to other potential mechanisms of action of TXA. In addition to its role in fibrinolysis, plasmin activates and inactivates a number of important procoagulant and anticoagulant molecules and interacts with cellular components involved in the hemostatic balance (26). Plasmin also plays roles in inflammation, angiogenesis, and wound healing, and TXA has been shown to have beneficial effects with respect to inflammatory (27, 28) and other responses (29) following ischemia reperfusion. It is not possible from available data to identify specific mechanism(s) of action that are involved in potential salutary or deleterious effects of TXA in trauma. As pointed out by others, mechanisms other than inhibition of fibrinolysis may be involved (6, 7, 30, 31). The potential importance of the complement system

(32) and impact of immune modulation (33) suggest that an inflammatory pathway may be involved in the observed effects of TXA. Other mechanisms may also be important. A better understanding of TXA mechanism of action will be important in understanding potential beneficial and negative effects and the optimal dosing regimens.

OTHER KNOWLEDGE GAPS

A number of other important questions remain. Factors such as optimal dosing, alternative routes of administration, interactions with various resuscitation and transfusion regimens, and interactions with additional hemostatic drugs, such as recombinant activated factor VIIa, prothrombin complex concentrates, and fibrinogen concentrate, remain to be determined. Metabolic clearance will also be important to understand. Tranexamic acid is cleared by the kidney in a manner that can vary based on patient status and surgical procedure (34). Factors such as polytrauma and hemorrhagic shock, which alters kidney function within 1 h in animal models (35), may also be important. Impaired renal function may alter the risk profile for a given dose of TXA, as has been observed for cephalosporins, which are also cleared by the kidney (36).

CONCLUSIONS

Recent studies have provided the most promising data to date for any drug to improve survival after traumatic hemorrhage. A number of important knowledge gaps remain, and our ability to provide additional information will allow the trauma community to refine and improve its ability to apply TXA in the safest and most effective manner. The prioritization of knowledge gaps is based on military requirements, which consider the austere combat environment, unique injury patterns and severity, and a generally young, healthy population. However, most of the identified knowledge gaps are applicable for both military and civilian trauma. At individual centers, expanded monitoring and laboratory analyses are strongly recommended and will be important in beginning to provide more information. At the larger scale, a targeted, prioritized research effort is needed to address key knowledge gaps and contribute to refinement of practice guidelines over time.

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